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fails to comply with the requirements of 37 C.F.R. §1.821 through §1.825 for the following reasons(s): The Examiner alleged that the text of the specification discloses nucleotide or amino acid sequences but the application does not contain a copy of the "Sequence Listing" in computer readable form (CRF).

The Examiner stated that applicant's response to the notice to comply with requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosure in Paper No. 7 filed 2/7/02 is acknowledged. The Examiner alleged that although applicant indicated in the response that a disk was submitted, none was entered in the application. The Examiner stated that applicant is required to re-submit a CRF of the sequence listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §1.821(e) or §1.821(f) or §1.821(g) or §1.825(b) or §1.825(d).

The Examiner stated that applicants must fully comply with the sequence rules for any response to this action to be considered fully responsive.

In response, applicants respectfully traverse the Examiner's above objection. In contrast to the Examiner's statement that applicants failed to submit a computer disk containing sequence listing, applicants respectfully direct the Examiner to a copy of the postcard attached hereto as **Exhibit 2**. Applicants respectfully point out that the above-identified postcard, date stamped February 7, 2002 by the Patent and Trademark Office,

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acknowledges receipt of applicant's computer disk containing CRF of Sequence Listing, paper copy of Sequence Listing, copy of Notice, and Statement. Nevertheless, in order to expedite prosecution of the subject application, applicants re-submit and attach hereto as Exhibit 3, a paper copy of the sequence listing, a computer disk containing a CRF of the sequence listing, and as Exhibit 4, a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. \$1.821(e) or \$1.821(f) or \$1.821(g) or \$1.825(b) or \$1.825(d). Applicants contend that these exhibits obviate the Examiner's above objection and respectfully request that the Examiner reconsider and withdraw such grounds of objection.

Copy of papers originally filed:

The Examiner stated that the papers filed on 2/702 (certificate of mailing dated 2/7/02) have not been made part of the permanent records of the United States Patent and Trademark Office (Office) for this application (37 CFR 1.52(a)) because of damage from the United States Postal Service irradiation process. The Examiner stated that the above-identified papers were not so damaged as to preclude the USPTO from making a legible copy of such papers. The Examiner stated that the Office has made a copy of these papers, submitted them for the originals in the file, and stamped that copy:

COPY OF PAPERS ORIGINALLY FILED

The Examiner stated that if applicant wants to review the

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accuracy of the Office's copy of such papers, applicant may either inspect the application (37 CFR 1.14(d)) or may request a copy of the Office's records of such papers (i.e., a copy of the copy made by the Office) from the Office of Public Records for the fee specified in 37 CFR 1.119(b)(4).

The Examiner stated that if the applicant does not consider the Office's copy of such papers to be accurate, applicant must provide a copy of the above-identified papers (except for any U.S. or foreign patent documents submitted with the aboveidentified papers) with a statement that such copy is a complete and accurate copy of the originally submitted documents. Examiner stated that if applicant provides such a copy of the above-identified papers and statement with THREE MONTHS of the mail date of this Office action, the Office will add the original mailroom date and use the copy provided by applicant as the permanent Office record of the above-identified papers in place of the copy made by the Office. The Examiner stated, otherwise, the Office's copy will be used as the permanent Office record of the above-identified papers made by the Office for examination The Examiner stated that this threeand all other purposes). month period is not extendable.

In response, applicants attach hereto as <u>Exhibit 5</u>, a copy of the above-identified papers, i.e. papers filed on December 12, 2001, and as <u>Exhibit 6</u>, a statement that such copy is a complete and accurate copy of the originally submitted documents. Applicants respectfully request that this copy of the original papers filed on December 12, 2001, be used as the permanent Office record of

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the above-identified papers for examination and all other purposes.

Election/Restrictions:

The Examiner stated that claims 2, 4 and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. The Examiner stated that applicant's election of Invention II in Paper No. 9 filed 4/29/02 is acknowledged. Examiner stated that the traversal is on the ground that claims of Invention II are not independent of Inventions I and III-IV and further that the claims of Invention II and Inventions I and III-IV allegedly do not define patentably distinct inventions. The Examiner stated that applicant's response/election 09/648,389 (Paper 9, dated 4/29/02) states, "Under M.P.E.P. §802.1. "independent" means "there is no disclosed relationship between the subjects disclosed, that is, they are unconnected in design, operation, and effect". The Examiner stated that it is assumed that application means M.P.E.P. §802.01. The Examiner alleged, furthermore, applicant has misquoted M.P.E.P. §802.1. M.P.E.P. §802.1 (August, 2001) properly states: "independent" means that there is no disclosed relationship between the two or more subjects disclosed, that is, they are unconnected in design, operation, or effect." The Examiner alleged that the applicants response recited "the claims of ... Invention II, ... drawn to a method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with a nucleic acid sequence (antisense sequence) as an inhibitor of Egr-1 protein are related to ... Inventions I and III-IV... drawn to a method for

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reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with an organic or inorganic compound, a peptide or an antibody as an inhibitor of Egr-1". The Examiner alleged that the method for reducing damage or vascular injury to an ischemic tissue by contacting cell of the tissue with a nucleic acid sequence, an organic or inorganic compound, a peptide or an antibody as inhibitors of Egr-1...are methods that are materially different and patentably distinct from each other, as each methods requires materials and method steps, technologies and search of a body of prior art, that are distinctly different from those required for each of the others. The Examiner alleged that the applicants recited "under M.P.E.P. §803, the Examiner must examine the application on the merits, even though it includes claims to distinct inventions, if the search and examination of an application can be made without There are two criteria for a proper requirement serious burden. for restriction, namely (1) the invention must be independent and distinct; AND (2) there must be a serious burden on the Examiner if restriction is not required". The Examiner alleged applicant has misquoted M.P.E.P. §803. The Examiner alleged M.P.E.P. §803 (August, 2001) properly states: "There are two criteria for a proper requirement for restriction, namely (1) the invention must be independent or distinct as claimed; AND (2) there must be a serious burden on the Examiner if restriction is not required". The Examiner alleged that distinctness is proven for claims in this relationship if the species are patentably distinct The Examiner alleged that the species of (M.P.E.P. §806.04(h)). the instant case are patentably distinct as being methods for reducing damage or vascular injury to an ischemic tissue by

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contacting cells of the tissue with a nucleic acid sequence, an organic or inorganic compound, a peptide or an antibody as inhibitors of Egr-1. The Examiner alleged that the inventions are deemed patentably distinct since there is nothing on this record to show them to be obvious variants. The Examiner stated that should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the The Examiner stated that in either instance, if the case. Examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. §103 of the other invention. The Examiner stated that the method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with a nucleic acid of Invention II and the methods of Inventions I and III-IV are related as processes of use. The Examiner alleged that the inventions can be shown to be distinct if: The process for using the product as claimed can be practiced with another materially different product (M.P.E.P. § 806.05(h)). The Examiner alleged that in the instant case, the method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with a nucleic acid of Invention II can be used as a method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with an organic compound of Invention I, for example. The Examiner stated that because these inventions are allegedly distinct for the reasons given above and have acquired a separate status in the art due to their divergent subject matter as shown by their

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classification, their capability of separate use and function, and because the search required for each of the Inventions I-IV is not required for each of the other Inventions, restriction for examination purposes as indicated is proper and final. The Examiner stated that claims 2, 4 and 8 are withdrawn form further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic linking claim. The Examiner stated that the applicant timely traversed the restriction (election) requirement in Paper No.9 filed 4/29/02. The Examiner stated that claims 1, 3, 5-7 and 9-27 will be examined as they read on the elected subject matter.

Rejection under 35 U.S.C. § 112, first paragraph:

The Examiner rejected claims 1, 3, 5-7 and 9-27 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method for reducing vascular injury during reperfusion of an ischemia-induced lung tissue, which comprises contacting the tissue with a nucleic acid of the sequence of SEQ 1, which inhibits (antisense) Eqr-1 before, during or does not reasonably provide after reperfusion, allegedly enablement for a method for reducing vascular injury during reperfusion of an ischemic tissue wherein the tissue is to be transplanted into a subject; wherein the tissue is a lung, a heart, a vein, an artery, a stomach, a colon, a liver, skin, an eye, a pancreas, a brain, a finger, a toe or limb; wherein the subject has suffered a stroke, or a myocardial infarction; wherein the subject is undergoing angioplasty, cardiac surgery, vascular surgery, or organ transplantation; wherein the vascular surgery is coronary artery surgery.

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The Examiner alleged that claims 1, 3, 5-7 and 9-27 are drawn to embrace a method for reducing vascular injury during reperfusion of an ischemic tissue, which comprises contacting tissue with a nucleic acid which inhibits (artisense) Egr-1, before, during or after reperfusion. The Examiner alleged that the instant invention specification provides general methodologies for determining whether tissue injury in Egr-1 null diminished would mice be in response to lung ischemia/reperfusion.

The Examiner alleged that Lee et al. (Science, 1996, 273:1219-21) disclose that Egr-1 null mice display luteinizing hormone deficiency (LDH) and female fertility. The Examiner alleged that Lee et al. further disclose that Egr-1 influences female reproductive capacity through its regulation of LDH-ß transcription (see Abstract).

The Examiner alleged that Topilko et al. (Molecular Endocrinology, 1998, 12:107-22) disclose multiple pituitary and ovarian defects in Egr-1 null mice. The Examiner alleged that Topiko et al. further disclose that mice homozygous for an Egr-1 mutation have a reduced body size, and both males and females are sterile.

The Examiner alleged that Murphy et al. (Circulation Research, 1999, 84:1469-1470) disclose that accumulation of Na⁺ during ischemia and early reperfusion leads, via Na⁺/Ca²⁺ exchange, to elevated Ca²⁺, resulting in myocardial damage (see Abstract).

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The Examiner alleged that Medrum (Journal of Surgical Research, 1997, 73:1-13) disclose that as Ca²⁺ increases, the phospholipid hydrolysis required to activated some protein kinase C (PKC) isoforms diminishes (see page 3, first column). The Examiner alleged that Medrum further disclose, ischemia and reperfusion induce myocardial damage, which is likely mediated, in part, by destructive inflammation (see page 7, second column).

The Examiner alleged that Yoshidome et al. (Journal of Surgical Research, 1999, 81:33-37) disclose that ischemia/reperfusion injury may lead to local and systemic organ dysfunction/injury (see Abstract). The Examiner alleged that Yoshidome et al. further disclose that macrophage inflammatory protein-2 (MIP-2) and KC, two potent chemokines, which cause neutrophil activation, exhibit increased expression in a lung ischemia/reperfusion model. The Examiner alleged that Yoshidome et al. assert, "it appears that MIP-2 and KC contribute to lung neutrophil accumulation and the associated pulmonary injury following hepatic ischemia/reperfusion."

The Examiner alleged that Santiago et al. (American Journal of Pathobiology, 1999 155:897-905) disclose that Egr-1 plays an important regulatory role in smooth muscle cell regeneration, but suggest future strategies directed at Egr-1 after injury (page 904, last paragraph). The Examiner alleged that this disclosure appears to indicate that much work needs to be done to elucidate the function of Egr-1 in vascular injury such that one of ordinary skill in the art would know how to target Egr-1 for reducing vascular injury or ischemia. The Examiner alleged that

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the specification as filed shows the effect of lung ischemia/reperfusion on survival times (mortality), arterial oxygenation, myeloperoxidase activity and lung edema (wet to dry The Examiner alleged that these examples fail to weight ratio). show, by correlation, the treatment of reducing vascular injury during reperfusion of an ischemic tissue via Egr-1 antisense inhibition. The Examiner alleged that these examples do not demonstrate that the deleterious effects observed in the prior avoided above were upon Egr-1 gene knockout art ischemia/reperfusion. The Examiner alleged that the specification is silent on the effect of Egr-1 antisense on male sterility, or female reproductive capacity. The Examiner alleged that the specification is further silent on the levels of Natand Ca2+, the PKC isoforms expressed, the myocardial condition and the expression, in vascular injury during reperfusion of an ischemic tissue such that contacting the tissue with a nucleic acid which inhibits (antisense) Egr-1, before, during or after reperfusion will reduce damage to the tissue.

The Examiner alleged that the specification as filed does not provide adequate guidance of examples that would show by correlation the practice of the instant invention without the need for undue trial and error experimentation. The Examiner alleged that the specification does not provide a meaningful nexus between an ischemic tissue and contact with an Egr-1 antisense such that interaction will reduce damage to the tissue. The Examiner alleged that it is unpredictable as to whether contact of an ischemic tissue of different lineages (e.g. brain or skin) with an Egr-1 antisense will reduce damage to the

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tissue. The Examiner stated that antisense oligonucleotides are greatly desirable biological agents for reasons well known in the art. The Examiner alleged, however, it is also well-known in the art that the design of antisense oligonucleotides as therapeutic agents is unpredictable because the biological effects could be non-specific in nature. The Examiner alleged that it is unpredictable that contact of ischemic tissues of different compositions (e.g. epithelial vs. keratinocyte) with an Egr-1 antisense will reduce damage to the tissue.

The Examiner alleged that the unpredictability of the art of antisense therapy in general further adds to the lack of enablement for the current invention. The Examiner alleged that Vol 23, Branch (TIBS February 1998) addresses unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack, this is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Nonantisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible

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to antisense molecules."; "Years of investigation can be required figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting , non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, .which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded form most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition in vivo is beginning to be explored....It is not yet clear whether in vitro screening techniques....will identify ODN's that are effective in vivo."

The Examiner alleged that Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges

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that remain before the use of antisense becomes routine in a The Examiner alleged that Jen et al. therapeutic setting. discuss the advances made in the art but also indicate that more progress needs to be made in the art. The Examiner alleged that in the conclusion of their view, Jen et al. assert, "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." The Examiner alleged that Jen et al. also stated "The key challenges to this field have been outlined above." The Examiner alleged it is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. The Examiner alleged a large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." The Examiner alleged it is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome

The Examiner alleged that one of ordinary skill in the art would have to engage in undue trial and error experimentation to develop a method for reducing damage to an ischemic tissue, which comprises contacting cells of the tissue with an Egr-1 antisense molecule. The Examiner alleged that in view of the unpredictability of the art, the quantity of experimentation required would include the testing of ischemic tissues from different lineages (e.g. stomach, or eye, or brain), the degree of ischemia (e.g. moderate or extreme) and the variability in

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contact time that would result in the reduced damage to the ischemic tissue...also to overcome the obstacles to antisense based on therapy exemplified in the references cited above. The Examiner alleged that undue experimentation would be required of one of ordinary skill in the art to make and use the claimed invention.

The Examiner alleged that one of ordinary skill in the art would require specific guidance on how to practice the current invention. The Examiner alleged that the current specification does not provide such guidance and one of ordinary skill in the art would be required to perform undue trial and error experimentation to practice the current invention. The Examiner alleged that the amount of experimentation would include overcoming the obstacle to routine antisense therapies as exemplified in the references discussed above.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the specification is enabled such that one of ordinary skill in the art could make and use the presently claimed invention. Specifically, applicants contend that the specification clearly teaches the role of Egr-1 in ischemia/reperfusion in a model of ischemic tissue and a method for reducing damage to an ischemic tissue by contacting an ischemic tissue with an inhibitor of Egr-1.

In support of the role of Egr-1 in ischemia/reperfusion, applicants respectfully direct the Examiner to the data recited in figure 5A which demonstrates that ischemia/reperfusion induces

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and activates Egr-1 in murine lung. Specifically, Northern blotting was performed on total RNA from control ischemia/reperfusion lung from wild-type mice which underwent left lung ischemia. See Figure 5A. The specification recites that "these data provide insight into a previously unidentified role for Egr-1 as a master switch regulating a range of effector mechanisms underlying ischemic stress." See page 48, lines 23-25.

In addition, the specification clearly teaches a method for reducing damage to an ischemic tissue by contacting an ischemic tissue with an inhibitor of Egr-1. Applicants respectfully direct the Examiner to Figures 12 and 13 which data demonstrate the effect of control (carrier) orEgr-1 antisense oligodeoxyribonucleotide on gas exchange and recipient survival following left lung transplantation and circulatory exclusion of the right (nontransplanted) lung. Regarding these data, the specification recites that "when antisense compound was given to the donor rat prior to lung transplantation, the function of the graft after transplantation (measured by arterial oxygenation in the recipient which depends entirely upon the transplanted lung) is improved only by the antisense Egr-1 oligodeoxyribonucleotide" and that "survival of the recipient rat following transplantation is improved only by the antisense Egr-1 oligoribonucleotide (figure 13)." See page 54, lines 5-12.

Therefore, applicants contend that the specification clearly teaches the role of Egr-1 in ischemia/reperfusion in a model of ischemic tissue and a method for reducing damage to an ischemic tissue by contacting an ischemic tissue with an inhibitor of Egr-

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1. Accordingly, the specification is enabled such that one of ordinary skill in the art could make and use the presently claimed invention.

Rejection under 35 USC §102(b):

The Examiner rejected claims 1-9, 11, 15 and 26 under 35 U.S.C. § 102(b) as being anticipated by Santiago et al. (American Journal of Pathobiology, 1999 155:897-905). The Examiner alleged that claims 1-9, 11, 15 and 26 are drawn to a method for reducing damage to an ischemic tissue, which comprises contacting the cells of the tissue, which comprises contacting cells of the tissue with a nucleic acid inhibitor (antisense) of Egr-1. Examiner alleged that Santiago et al. disclose that rat vascular smooth muscle cell (SMC) regrowth after injury is inhibited by directly targeting Egr-1 via antisense (see page 902, first The Examiner alleged that Santiago et al. further paragraph). disclose an antisense oligonucleotide (identical to SEQ ID NO:1) that inhibits Egr-1 (See Santiago et al., Table 1). The Examiner alleged that this antisense oligonucleotide contains all of the structural limitations of SEQ ID NO:1 of the instant invention.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that Santiago et al. fails to disclose each and every element of the presently claimed invention. Therefore, claims 1-9, 11, 15 and 26 are not anticipated by Santiago et al. Specifically, while Santiago et al. may at most disclose that an Egr-1 PS-ODN may inhibit smooth muscle cell proliferation and regrowth after mechanical injury in vitro, it neither discloses nor suggests the claims of the

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present invention, i.e. a method for reducing damage to an ischemic tissue with an inhibitor of Egr-1.

Initially, applicants respectfully direct the Examiner to claim 1 which recites as follows:

A method for reducing damage to an **ischemic tissue** which comprises contacting cells of the tissue with an inhibitor of Early Growth Response Factor - 1 Protein (Egr-1) [emphasis added].

The specification recites that "activation of the zinc finger transcription factor Early growth response (Egr)-1, initially linked to developmental processes, is shown here to function as a master switch tripped by ischemia" See page 39, lines 16-18. Further, the specification recites that "these data provide insight into a previously unidentified role for Eqr-1 as a master switch regulating a range of effector mechanisms underlying ischemic stress" [emphasis added] See page 48, lines 23-25. addition, the specification recites that "our data suggest that short-term antagonism of Egr-1 may provide an unexpected therapeutic target to diminish maladaptive host responses incited by acute ischemia." See page 50, lines 2-4. Accordingly, applicants contend that the specification demonstrates a previously unidentified role for Egr-1 in response to ischemia, and that antagonism of Egr-1 may provide a therapeutic target for amelioration of Egr-1 mediated ischemic damage.

In contrast to the presently claimed invention, Santiago et al.

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recite that "smooth muscle cell (SMC) proliferation is a key event in renarrowing of blood vessels after balloon angioplasty" and that "mechanical injury imparted to the arterial wall in experimental models induces the expression of the early immediate gene, egr-1" [emphasis added] See page 897, first paragraph. Further, Santiago et al. recite that in response to such mechanical injury "we used antisense stragtegies in vitro to inhibit rat vascular SMC proliferation." See page 897, first paragraph. Accordingly, applicants contend that while Santiago et al. may at most disclose that an Egr-1 PS-ODN may inhibit smooth muscle cell proliferation and regrowth after mechanical injury in vitro, it neither discloses nor suggests the claims of the present invention, i.e. a method for reducing damage to an ischemic tissue with an inhibitor of Egr-1.

Therefore, applicants contend that Santiago et al. fails to disclose each and every element of the presently claimed invention and that claims 1-9, 11, 15 and 26 are not anticipated. Accordingly, applicants contend that this argument obviates the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw such grounds of rejection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and objection and earnestly solicit allowance of the now pending claims, i.e. claims -----

If a telephone interview would be of assistance in advancing

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prosecution of the subject application, applicants' undersigned attorney invite the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

John P/ White Registration No. 28,678 Attorney for Applicant(s) Cooper & Dunham, LLP 1185 Avenue of the Americas New York, New York 10036 (212) 278-0400